## REMARKS

This amendment is in response to the Office Action mailed July 7, 2006 in the above-identified application. Applicants request a three-month extension of time and enclose the relevant fee. Also enclosed is a Request for Continued Examination and the relevant fee for the RCE.

Claims 20, 22, and 24-26 are currently under examination. These claims have been rejected for lack of enablement pursuant to 35 USC §112, ¶1. By this amendment, Claim 20 has been amended to incorporate the subject matter of Claim 22 therein. Claim 22 has been canceled. This amendment should not necessitate a new search by the Examiner.

The Examiner argues that the specification, while enabling the production of antibodies against an annexin protein, does not enable immunizing a host suffering from cancer, e.g. lung carcinoma, for the purposes of immunotherapy.

The Examiner finds the state of the art at the date of invention to be highly unpredictable with respect to the ability to provide effective therapeutic vaccination against cancers and, thus, requires that the specification provides considerable support and embodiment.

The Examiner has cited several papers to support the argument that one of skill in the art would conclude that immunotherapy of tumors is highly unpredictable and, that even when good antibody production is achieved, there is seldom an anti-tumor effect. While this may be true for some tumor types, in the case of annexin proteins in lung cancer, the instant specification in combination

with a current understanding of the art provides sufficient support for one skilled in the art to practice the invention as presently claimed without undue experimentation.

In establishing whether the skilled artisan would be required to perform undue experimentation to carry out the presently claimed invention, various steps involved in development of an immunotherapy must be considered and what teaching, if any, is provided in the specification and available art.

To develop an immunotherapeutic in accordance with the claimed invention one must:

(a) define the immunogen

(b) define an adjuvant and route of administration

(c) establish a minimum effective dose

(d) establish a maximum tolerated dose

(e) demonstrate efficacy in an animal model system and/or man

As discussed above, the threshold for undue experimentation depends on the level of predictability in the art and the level of skill of those in the art. While the Examiner contends that the art is unpredictable, Applicants respectfully contend that, in this case, the art should be considered more predictable and, thus, even a considerable level of routine experimentation would not constitute "undue experimentation." (see, e.g. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F. 2d 1367) (Fed. Cir. 1986).

Accordingly, when considering the various steps above, applicants maintain that the specification, in combination with other documents in the art,

provide the necessary guidance and grounds for success in arriving at the presently claimed invention. The immunogen is well characterized in the specification as being an Annexin I or Annexin II protein, which may be extracted from a patient's own tumor or produced at much larger scale by culturing cells that are representative of the targeted tumor. The precise nature of the immunogen is further characterized by the inventors own publication of 2001 which clearly states "immunoreacticity was dependent on N-glycosylation " and that "a potential N-linked glycosylation site is present at positions 42 and 61 from the N terminus of Annexins I and II, respectively" [Brichory et all. PNAS, 98: 9824-9829]. Brichory et al. also point out that it was known that Annexin II-derived peptides are presented on MHC class II molecules in melanoma and suggest that a similar mechanism is present in lung cancer, providing a strong support for the likely evolution of the anti-annexin humoral immune response. In the instant specification, the inventors disclose production of Annexin I and Annexin II proteins in the A549 human lung adenocarcinoma epithelial cell line. Both live cells and whole cell lysates of A549 cells are commercially available.

While there are many adjuvants known in the art, selection of the optimal preparation is no more than a routine endeavor. In the field of cancer immunotherapy, a number of adjuvants have been proposed, including the BCG adjuvant more commonly used in tuberculosis vaccination. The inventors provide clear teaching as to the nature of adjuvants suitable for use with the invention at page 20 of the specification.

In addition, adjuvant support in the form of cytokines has been proposed. In regard to the present invention, the inventors demonstrated in their 2001 PNAS paper that increased levels of the inflammatory response cytokine, interleukin 6 (IL-6), correlated significantly with autoantibody response. Brichory et al. conclude by saying "Our findings led us to propose a mechanism for the development of autoantibodies against certain proteins in cancer, whereby host factors such as cytokines may affect the level and cellular distribution of a potential antigen, the presentation of specific polypeptides, and also modulate the immune response in other ways." Accordingly, one of skill in the art would have all the necessary means at their disposal to prepare suitable immunotherapeutic formulations.

Determination of routes of administration for cancer immunotherapeutics is also well known in the art. Typically immunization is performed through intramuscular or intravenous administration. The specification teaches these and other methods of administration on page 20.

The inventors clearly state on page 7: "the identification of autoantibodies to annexin protein antigen associated with particular cancers provides a basis for immunotherapy of the disease." Further evidence of the validity of this approach was recently published by Sharma et al., Exp. Mol. Pathol. 2006, in press (copy attached), who demonstrated inhibition of a mouse lung cancer by administration of anti-Annexin II antibodies in passive immunization. Such information available in the art, in addition to the teachings of the specification, provide

reasonable grounds for the success of one skilled in the art in developing lung cancer immunotherapy based on Annexins I and/or II as presently claimed.

The literature also contains other reports showing positive outcomes of cancer immunotherapy. For example, Gilewski et. al., Proc. Natl. Aead. Sci. 98: 3270-3275 (2001) reported stimulation of an antibody responses to the tumor antigen globo H in women with breast cancer using a similar approach to that proposed by the inventors for annexin vaccines in lung cancer. A predominantly IgM response was initiated with antibodies mediating killing of glob H-bearing tumor cells in vitro. The data were considered sufficient to justify incorporation of globo H into a polyvalent breast cancer vaccine.

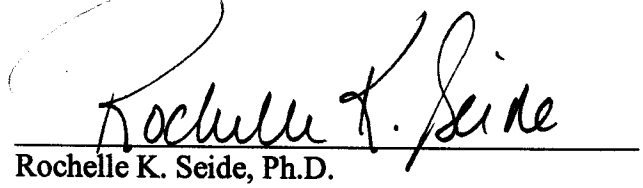
It is believed that the amendments presented herein to the claims, together with the above arguments, show that the presently claimed invention is enabled and place the present application in condition for allowance. Applicants respectfully request issuance of a Notice of Allowance.

Payment of the extension fee is to be made according to the Credit Card Payment Form attached herewith. Applicants believe that no additional fees are required in connection with this response. However, if additional fees are required, the Commissioner is hereby authorized to charge any additional

payment, or credit any overpayment, to Deposit Account No. 01-2300,

**referencing Docket Number 108140.00022.**

Respectfully submitted,



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